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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,785	10/03/2005	Marco Cattaruzza	DEBE:053US	1068

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EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/527,785	CATTARUZZA ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *4-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2 and 3* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/3/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions/Status

Applicant's election without traverse of Group I, claims 1-3, in the reply filed on 7 November 2006 is acknowledged. Also acknowledged is applicants' election of SEQ ID NO:17 and its complement, SEQ ID NO:18.

Claims 1–10 are pending. Claims 4–10 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 7 November 2006.

Claims 1–3 are examined herein.

Claim Objections

Claims 1–3 are objected to for reciting non-elected subject matter. Specifically, the claims recite SEQ ID Nos. 1-16 and 19–34, which are inventions non-elected, and are currently withdrawn from consideration pursuant to 37 CFR 1.142(b) there being no allowable generic or linking claim.

Applicant is requested to amend the claims to remove the non-elected subject matter.

Sequences

The instant application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through

1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

The claims and description do not comply with 37 CFR §1.821(d), which states:

> 37 CFR § 1.821 Nucleotide and/or amino acid sequence disclosures in patent applications –
>
> (a) Nucleotide and/or amino acid sequences as used in §1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides.
>
> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

In the instant case, the nucleic acid sequence set forth in Fig. 1 does not have a SEQ ID NO: identifier as currently required by 37 CFR § 1.821. Applicant is requested to amend the instant application to provide the corresponding SEQ ID NO: identifier either in the drawing itself or in the Brief Description of the Drawing. Additionally, for completeness, Applicants are advised to review the entire disclosure for compliance with 37 CFR §1.821(d).

Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2 and 3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

Claim 2 is drawn to a decoy oligonucleotide formulated as a pharmaceutical agent. The "pharmaceutical agent" language in combination with the disclosure at pages 13-16 teaching the use of the decoy oligonucleotides for the prevention or therapy of atherosclerosis as well as several other diseases, including chronic inflammatory and/or autoimmune diseases such as rheumatoid arthritis, diabetes type I and II and their consequential diseases, requires that these claims be evaluated to determine whether the specification teaches how to use these oligonucleotides, specifically the double stranded oligonucleotide comprising SEQ ID NO:17

and 18, for treating and/or preventing all these diseases in any patient, including mammals such as humans.

Claim 3 is drawn to a method for the prevention or therapy of several different diseases, as recited in claim 3, including bacterial infections, herpes, and human immunodeficiency viruses.

Adequate support does not exist in the instant application enabling one of ordinary skill in the art to use the instantly claimed double-stranded decoy oligonucleotide to treat and/or prevent each of these diseases. As explained below, neither the prior art nor the instant application shows or provides any evidence by way of example or adequate representation that the instant decoy oligonucleotide provides any therapeutic effect against these particular diseases, much less that the decoy oligonucleotide is capable of preventing any of these diseases. Furthermore, the prior art suggests that the state of the prior art with regard to nucleic acid delivery and uptake into cells in vivo in therapeutic amounts to produce the desired treatment effect is unpredictable. There is evidence in the prior art, then, to doubt the objective truth of the statements in the specification, specifically those assertions at pages 13 and 16 and in claim 3 that the disclosure provided in the instant application is sufficient to enable one of skill in the art to use the claimed decoy oligonucleotide without undue experimentation to treat and prevent these diseases.

Problems related to the pharmaceutical use of nucleic acids, including double stranded oligonucleotides, were well known in the art at the time of invention. Such problems include the

inability to routinely deliver an effective concentration of a specific nucleic acid into a target cell, such that a target gene is inhibited to a degree necessary to produce a therapeutic effect.

Jen et al. (2000) *Stem Cells* 18:307-319 teach that

> "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive." (page 313, second column, second paragraph):

Opalinska et al. (2002) *Nature Reviews* 1:503-514 teach that

> "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" and in column 2 of the same page, "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded." (page 511)

Thus, the pre- and post-filing art indicates that the art of in vivo delivery of single- and double stranded nucleic acids for selectively inhibiting gene expression in animals and humans is unpredictable.

In view of the express teachings of the post-filing art suggesting that in vivo delivery of nucleic acids is unpredictable, it is essential that the instant application provide enabling disclosure showing how to use the invention in any and all animals. A review of the instant application fails to find adequate representations or guidance exemplifying the use *in vivo* of the claimed pharmaceutical preparations and decoy oligonucleotides. Although, applicants clearly discuss possible routes of delivery and methods of administration of nucleic acids (pp. 28 and 29,

for example), these teachings are general in nature, and do not teach the ordinary artisan how to effectively deliver double-stranded decoy nucleic acids into target tissues and cells *in vivo* in an amount effective to affect nitric oxide production and/or treat and prevent any of the diseases now recited in claim 3 and on page 16 of the specification.

Thus, the amount of disclosure is insufficient given the level of unpredictability in the art. For example, the instant application does not appear to teach one of skill in the art how to effectively target tissues and cells in the brain. Similarly, while the instant application is enabling for the use of double stranded nucleic acids to transfect cells in culture, it does not enable the use of these molecules *in vivo* in a way that would reasonable enable one of skill in the art to use the invention so as to obtain a desired result, e.g., phenotype or outcome in an individual.

A review of the instant application finds at least one working example of the use of decoy oligonucleotides in vitro in cultured endothelial cells (pp.36-38); however, these examples are directed to the cellular uptake and inhibition of transcription factor activity *in vitro* (in cell culture). The examples do teach one of skill how to deliver decoy oligonucleotides into cells *in vivo* to treat or prevent any particular condition. That is, no technical guidance or exemplary disclosure is provided regarding the use of the claimed pharmaceutical compositions for targeting genes in cells and tissues in living organisms, including any mammal.

As the post-filing art indicates, in culture results are not readily extrapolated to *in vivo* applications. Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

The primary factors appear to be delivery, uptake, stability, and biological effect in host organisms, which cannot be predicted *a priori* based on cell culture experiments.

While certain working examples adequately demonstrate and enable the use of certain oligonucleotides in specific circumstances, and while eNOS expression or lack thereof appears to be correlated with cardiovascular disease, reasonable correlation does not exist for treatment and prevention of all the diseases now recited in claim 3. That is, the disclosure is not commensurate in scope with the large number and variety of therapeutic methods now claimed.

Given the unpredictability in the art, the skilled artisan would require specific guidance to practice use the claimed oligonucleotide to treat one or more disorders *in vivo* in any given patient. That is, specific guidance would be required to teach one of skill in the art how to use the claimed compositions to produce a positive effect in a patient.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of using nucleic acids in therapeutic applications in any organism to practice the full scope of the methods now claimed. The teachings of the prior art does not provide that guidance, such that the skilled artisan would be able to use the claimed pharmaceutical agent in the manner disclosed to produce the intended effects of treating and preventing the disclosed diseases.

Thus, considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to use the claimed invention commensurate with the claims scope.

Given these teachings, the skilled artisan would not know *a priori* whether introduction of oligonucleotides *in vivo* by the broadly disclosed methodologies of the instant invention, would result in the oligonucleotide reaching the proper cell in a sufficient concentration and remaining for a sufficient time to provide successful inhibition of expression of a target gene. In fact, the state of the art is such that successful delivery of oligonucleotide sequences *in vivo* or *in vitro*, such that the polynucleotide or oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of using nucleic acids in therapeutic applications in any organism. The teachings of the prior art does not provide that guidance, such that the skilled artisan would be able to use the claimed pharmaceutical compositions in the manner disclosed to produce the intended effects of treating the disclosed diseases.

Thus, considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to use the claimed invention commensurate with the claims scope.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement. Removing the "pharmaceutical" language from claim 2 would overcome this rejection with regard to claim 2.

Moreover, with regard to claim 3, particular attention is given to the word "prevention" as it is used therein. "Prevent" is an absolute concept, defined by the American Heritage Dictionary, 3rd ed. as "to keep from happening" and "to counter in advance." Reasonable correlation must exist between the claims and the enablement set forth. Sufficient evidence and technical guidance does not exist in the instant application or the prior art enabling one of skill in the art at the time the application was filed to prevent any of the disorders and diseases in claim 3 from happening at all.

Allowable Subject Matter

The prior art searched to date does not teach or reasonably suggest double stranded decoy oligonucleotides comprising SEQ ID No: 17 or its complement, SEQ ID NO:18.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LVW
November 29, 2006
Examiner, Art Unit 1635

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER